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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
EWOLDT, GERALD R	

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 03/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/992,524	VASQUEZ ET AL.	
	Examiner	Art Unit	
	G. R. Ewoldt, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of Group I, Claims 14-24, filed 9/27/04, without traverse, is acknowledged.

2. Claims 1-13 have been canceled.

Claims 14-24 are pending and under examination.

3. The specification is objected to for the introduction of new matter into the specification. In the amendment, filed 1/22/03, Applicant removed the word "mature" from the Brief Description of Figures 2A and 2B. Said removal changes the scope of the description, thus, comprising the introduction of new matter into the specification.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 18-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the laboratory designation "the human EU immunoglobulin" is vague and indefinite as laboratory designations cannot be held constant throughout the art. Applicant is advised to claim the immunoglobulin by SEQ ID NOS:.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for,

a humanized immunoglobulin comprising a V_L of SEQ ID NO:6 and a V_H of SEQ ID NO:8,

does not reasonably provide enablement for,

a humanized immunoglobulin comprising a V_L of SEQ ID NO:6 and a V_H having at least 90% sequence identity to SEQ ID NO:8.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Regarding novel products relating to biological processes, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling (MPEP 2164.03)". The MPEP further states that physiological activity, which would encompass biologically active compositions including antibodies, can be considered inherently unpredictable. Given the inherent unpredictability of the art, the requirement for a certain amount of enablement beyond mere assertion is not unreasonable.

A review of the specification discloses just one functional humanized antibody of the claims, HuZAF. HuZAF appears to consist of the V_L of SEQ ID NO:6 and a V_H of SEQ ID NO:8; no examples comprising changes to the V_H of SEQ ID NO:8 are disclosed. A further review of the specification discloses that the specification discourages said changes.

"Usually the CDR regions in humanized antibodies are substantially identical, and more usually, identical to the

corresponding CDR regions in the mouse antibody from which they were derived. Although not usually desirable, it is sometimes possible to make one or more conservative amino acid substitutions of CDR residues without appreciably affecting the binding affinity of the resulting humanized immunoglobulin. Occasionally, substitutions of CDR regions can enhance binding affinity."

"Other than for the specific amino acid substitutions discussed above, the framework regions of humanized immunoglobulins are usually substantially identical, and more usually, identical to the framework regions of the human antibodies from which they were derived. Of course, many of the amino acids in the framework region make little or no direct contribution to the specificity or affinity of an antibody. Thus, many individual conservative substitutions of framework residues can be tolerated without appreciable change of the specificity or affinity of the resulting humanized immunoglobulin" (page 11).

A reasonable interpretation of these teachings is that while certain amino acid substitutions are tolerated, they are not advised, and certainly multiple substitutions, particularly within the CDRs, would not be expected to produce a functional antibody.

Note that the polypeptide sequence of SEQ ID NO:8 is 135 amino acid residues long; accordingly, said sequence could incorporate 13 substitutions and still fall with the 90% variation allowed for the antibody of Claim 17. Further note that there is no limitation as to which residues can be substituted and which cannot. Thus, an antibody absent *all* of the amino acids of CDR1 (5 residues long) and *all* of the residues of CDR3 (8 residues long) could be encompassed by the claims. Clearly, by Applicant's own teachings, such an antibody would not be expected to bind IFNγ and thus, would not be enabled for its intended use. Also note that the specification includes essentially no specific guidance as to which amino acid residues can be substituted and which cannot. Accordingly, the skilled artisan is left with only the method of trial-and-error in determining which amino acids might be substituted and which might not. As methods of trial-and-error comprise no particular expectation of success, said methods are considered to be unpredictable and requiring of undue experimentation.

A review of the prior art shows that substituting amino acids within an antibody H chain can be highly unpredictable and generally produces a non-functional antibody. See, for example, Chen et al. (1992). The reference teaches that when 46 random point mutations were introduced into an antibody, 20 non-functional antibodies, 6 reduced-function antibodies, and no increased-function antibodies were produced. The reference further teaches that as the number of mutations increases, so does the percentage of non-functional antibodies.

Accordingly, given the teachings of both the specification and the prior art, it is the Examiner's position that the limited disclosure of the instant specification is insufficient support for the antibodies of the instant claims. In view of the quantity of experimentation necessary, the lack of sufficient working examples, the unpredictability of the art, and the lack of sufficient specific guidance in the specification, it would take undue trials and errors to practice the claimed invention.

8. Claims 17 and 21-23 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Under *Vas-Cath, Inc. v. Mahurkar* , 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession* of the invention, and that the invention, in that context, is whatever is now claimed.

There is insufficient written description to show that Applicant was in possession of a V_H having at least 90% sequence identity to SEQ ID NO:8.

The specification discloses only the V_H of SEQ ID NO:8. The claims however, encompass an essentially unlimited genus of substituted antibodies, none of which are disclosed. As the specification fails to disclose which amino acid residues might accept which substitutions, and which might not, it is clear that the specification discloses only the required function of

the antibody of the instant claims, and not its actual structure. Accordingly, one of skill in the art would conclude that the specification fails to disclose a representative number of species to describe the claimed genus. See *Eli Lilly*, 119 F.3d 1559, 43 USPQ2d 1398.

9. Claims 14-23 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. This is a new matter rejection.

The specification and the claims as originally filed do not provide support for the invention as now claimed, specifically, the recitation of "mature light chain variable region" in Claims 14, 15, and 17.

Applicant's amendment, filed 1/22/03, asserts that support for the new limitation "is readily apparent" from comparing the sequences of Figures 1A and 2A in the instant specification and Figure 32A in WO 92/11018. Applicant indicates that the WO document has been incorporated by reference.

Applicant is advised that the sequence of Figure 32A in the WO document is neither the sequence of Figure 1A nor Figure 2A of the instant application, accordingly, the sequence of the WO document cannot support any changes to the description of the sequences of the instant application. Further, the generic "incorporation by reference" of the jumbo WO document would still be insufficient in the instant case as the WO document is not cited in the instant specification in the context of describing a description of the sequences of SEQ ID NOS:2 or 6 of the instant application.

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA

1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

11. Claims 14-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-8 of U.S. Patent No. 6,329,511. Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims recite a humanized immunoglobulin version of the mouse AF2 antibody and encompass the antibodies encoded by SEQ ID NOS:6, 8, and 10. Note that Claims 14, 15, and 17 of the instant application are more generic than the claims of the '511 patent, i.e., they lack the limitation that the antibody bind human IFNγ, or have just 90% sequence identity, however, the antibodies of the '511 patent comprise species of the antibodies of the instant application and render them obvious.

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Gerald Ewoldt whose telephone number is (571) 272-0843. The examiner can normally be reached Monday through Thursday from 7:30 am to 5:30 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841.

Please Note: Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov.

Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

3/8/05

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